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<p>(21) International Application Number: PCT/US97/18177</p> <p>(22) International Filing Date: 7 October 1997 (07.10.97)</p> <p>(30) Priority Data:</p> <table border="0"> <tr> <td>60/028,105</td> <td>9 October 1996 (09.10.96)</td> <td>US</td> </tr> <tr> <td>60/028,106</td> <td>9 October 1996 (09.10.96)</td> <td>US</td> </tr> <tr> <td>60/029,255</td> <td>25 October 1996 (25.10.96)</td> <td>US</td> </tr> <tr> <td>60/035,202</td> <td>10 January 1997 (10.01.97)</td> <td>US</td> </tr> <tr> <td>60/035,366</td> <td>10 January 1997 (10.01.97)</td> <td>US</td> </tr> <tr> <td>60/048,987</td> <td>9 June 1997 (09.06.97)</td> <td>US</td> </tr> <tr> <td>60/050,949</td> <td>13 June 1997 (13.06.97)</td> <td>US</td> </tr> <tr> <td>08/898,715</td> <td>22 July 1997 (22.07.97)</td> <td>US</td> </tr> </table> <p>(71) Applicant: SYMYX TECHNOLOGIES [US/US]; 3100 Central Expressway, Santa Clara, CA 95051 (US).</p> <p>(72) Inventors: McFARLAND, Eric, W.; 607 N. Third Street, San Jose, CA 95112 (US). ARCHIBALD, William; 2323 Summit Drive, Hillsborough, CA 94010 (US).</p> <p>(74) Agents: BECK, David, G. et al.; Townsend and Townsend and Crew LLP, 8th floor, Two Embarcadero Center, San Francisco, CA 94111 (US).</p>	60/028,105	9 October 1996 (09.10.96)	US	60/028,106	9 October 1996 (09.10.96)	US	60/029,255	25 October 1996 (25.10.96)	US	60/035,202	10 January 1997 (10.01.97)	US	60/035,366	10 January 1997 (10.01.97)	US	60/048,987	9 June 1997 (09.06.97)	US	60/050,949	13 June 1997 (13.06.97)	US	08/898,715	22 July 1997 (22.07.97)	US	<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
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<p>(54) Title: INFRARED SPECTROSCOPY AND IMAGING OF LIBRARIES</p> <p>(57) Abstract</p> <p>Methods and apparatus for screening diverse arrays of materials using infrared imaging techniques are provided. Typically, each of the individual materials on the array will be screened or interrogated for the same material characteristic. Once screened, the individual materials may be ranked or otherwise compared relative to each other with respect to the material characteristic under investigation. According to one aspect, infrared imaging techniques are used to identify the active sites within an array of compounds by monitoring the temperature change resulting from a reaction. This same technique can also be used to quantify the stability of each new material within an array of compounds. According to another aspect, identification and characterization of condensed phase products is achieved, wherein library elements are activated by a heat source serially, or in parallel. According to another aspect, a Fourier transform infrared spectrometer is used to rapidly characterize a large number of chemical reactions contained within a combinatorial library.</p> <div data-bbox="714 1050 1396 1638"> </div>																									

INFRARED SPECTROSCOPY AND IMAGING OF LIBRARIES

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CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of commonly assigned U.S. Patent Application Serial No. 08/898,715, filed July 22, 1997, and a continuation-in-part of commonly assigned, co-pending U.S. Provisional Applications Serial Nos. 60/050,949,
10 filed June 13, 1997; 60/028,106, filed October 9, 1996; 60/029,255, filed October 25, 1996; 60/035,366, filed January 10, 1997; 60/048,987, filed June 9, 1997; 60/028,105, filed October 9, 1996; and 60/035,202, filed January 10, 1997; the complete disclosures of which are incorporated herein by reference for all purposes.

This application is also related to commonly assigned, co-pending U.S.
15 Patent Applications Serial Nos. 08/327,513, filed October 18, 1994, 08/438,043, filed May 8, 1995, and 08/841,423, filed April 22, 1997; commonly assigned U.S. Provisional Application Serial No. 60/016,102, filed July 23, 1996; and PCT Application No. WO 95/13278, filed October 18, 1995; the complete disclosures of which are incorporated herein by reference for all purposes.

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FIELD OF THE INVENTION

The present invention generally relates to methods and apparatus for rapidly screening an array of diverse materials which have been created at known locations on a single substrate surface, and in particular to the combinatorial synthesis and
25 characterization of libraries of diverse materials using IR imaging and spectroscopy techniques.

BACKGROUND OF THE INVENTION

The discovery of new materials with novel chemical and physical properties
30 often leads to the development of new and useful technologies. Currently, there is a tremendous amount of activity in the discovery and optimization of materials, such as superconductors, zeolites, magnetic materials, phosphors, catalysts, thermoelectric materials, high and low dielectric materials and the like. Unfortunately, even though the

for performing light-directed, spatially-addressable synthesis techniques (Fodor *et al.*, PCT Publication No. WO 92/10092, the teachings of which are incorporated herein by reference for all purposes).

Using these various methods, arrays containing thousands or millions of
5 different elements can be formed (U.S. Patent Application No. 08/805,727, filed December 6, 1991, the complete disclosure of which is incorporated herein by reference for all purposes). As a result of their relationship to semiconductor fabrication techniques, these methods have come to be referred to as "Very Large Scale Immobilized Polymer Synthesis," or "VLSIPS™" technology. Such techniques have met with substantial
10 success in screening various ligands such as peptides and oligonucleotides to determine their relative binding affinity to a receptor such as an antibody.

The solid phase synthesis techniques currently being used to prepare such libraries involve the sequential coupling of building blocks to form the compounds of interest. For example, in the Pirrung *et al.* method polypeptide arrays are synthesized on
15 a substrate by attaching photoremovable groups to the surface of the substrate, exposing selected regions of the substrate to light to activate those regions, attaching an amino acid monomer with a photoremovable group to the activated region, and repeating the steps of activation and attachment until polypeptides of the desired length and sequence are synthesized. These solid phase synthesis techniques cannot readily be used to prepare
20 many inorganic and organic compounds.

In PCT WO 96/11878, the complete disclosure of which is incorporated herein by reference, methods and apparatus are disclosed for preparing a substrate with an array of diverse materials deposited in predefined regions. Some of the methods of deposition disclosed in PCT WO 96/11878 include sputtering, ablation, evaporation, and
25 liquid dispensing systems. Using the disclosed methodology, many classes of materials can be generated combinatorially including inorganics, intermetallics, metal alloys, and ceramics.

In general, combinatorial chemistry refers to the approach of creating vast numbers of compounds by reacting a set of starting chemicals in all possible combinations.
30 Since its introduction into the pharmaceutical industry in the late 80's, it has dramatically sped up the drug discovery process and is now becoming a standard practice in the industry (*Chem. Eng. News* Feb. 12, 1996). More recently, combinatorial techniques have been successfully applied to the synthesis of inorganic materials (G. Briceno *et al.*,

ring-down absorption spectroscopy as well as conventional methods such as GC/MS, are excluded because of poor sensitivities, non-universal detectability, and/or slow response. Therefore an apparatus and methodology for screening a substrate having an array of materials that differ slightly in chemical composition, concentration, stoichiometry, and/or thickness is desirable.

SUMMARY OF THE INVENTION

The present invention provides methods and apparatus for the rapid characterization and analysis of an array of materials using infrared imaging and spectroscopy techniques. Typically, each of the individual materials on the array will be screened or interrogated for the one or several material characteristics. Once screened, the individual materials may be ranked or otherwise compared relative to each other with respect to the material characteristic under investigation. Materials that can be compared using the methods and apparatus of the present invention include, for example liquids, dissolved organic or inorganic molecules, covalent network solids, ionic solids and molecular solids. In particular, the present invention is directed to characterization systems utilizing thermal imaging and infrared spectroscopic imaging.

According to one aspect of the present invention, infrared imaging techniques are used to identify the active compounds within an array of compounds by monitoring temperature change in the vicinity of the compound. Temperature change results from a reaction, either exothermic or endothermic in nature, and may be localized to specific compounds within the library as well as the region of the substrate adjacent to the compounds in question. This same technique can also be used to quantify the stability of each new material within an array of compounds by observing the temperature change as a function of time. By measuring the decay of activity through the change in temperature over time for each site, the lifetime of catalysts, for example, can be quantified.

According to another aspect of the invention, identification and characterization of the condensed solid or liquid phase products is achieved, wherein library elements are characterized by their specific infrared absorption or reflectance. Such materials may be the product of reactions, for example, in the gas phase polymerization of ethylene to condensed phase polyethylene or in the hydrolysis of liquid dimethyldichlorosilane to elastomeric polydimethylsiloxane. In one embodiment specific

polymerization reaction at a predefined pressure and temperature;

Fig. 5 depicts a thermal map of a polymerization reaction for 61 elements in a library of elements within a pressurized reaction chamber;

Fig. 6 graphically illustrates the thermal evolution as a function of time for the polymerization reactions of eleven wells of a library;

Fig. 7 depicts an infrared source irradiating a library of compounds on an infrared transparent substrate according to the invention;

Fig. 8 depicts a polychromatic source irradiating a library of compounds on an infrared transparent substrate according to the invention; and

Fig. 9 depicts a schematic of an IR imaging system according to the invention.

DETAILED DESCRIPTION OF THE INVENTION

Glossary

The following terms are intended to have the following general meanings as used herein.

Substrate: A substrate is a material having a rigid or semi-rigid surface. In many embodiments at least one surface of the substrate will be substantially flat. In some embodiments the substrate will contain physical separations between synthesis regions for different materials. Suitable physical separations include, for example, dimples, wells, raised regions, and etched trenches. According to other embodiments, small beads or pellets may be provided on the surface, either alone or within substrate surface dimples. The surface area of the substrate is designed to meet the requirements of a particular application. Typically, the surface area of the substrate is in the range of 1 cm² to 400 cm². However, other sizes may be used with the present invention, for example surface areas as small as 0.001 cm² or as large as 10 m² are possible.

Predefined Region: A predefined region is a localized area on a substrate that is, was, or is intended to be used for the formation of a specific material. The predefined region may be referred to, in the alternative, as a "known" region, a "reaction" region, a "selected" region, or simply a "region." The predefined region may have any convenient

source. Alternatively, the resulting material may comprise a layer, blend or mixture of components on a predefined region of the substrate. The resulting materials are screened for specific properties or characteristics to determine their relative performance.

5 Mixture or Blend: The term mixture or, interchangeably, blend refers to a collection of molecules, ions, electrons, or chemical substances. Each component in the mixture can be independently varied. A mixture can consist of two or more substances intermingled with no constant percentage composition, wherein each component may or may not retain its essential original properties, and where molecular phase mixing may or
10 may not occur. In mixtures, the components making up the mixture may or may not remain distinguishable from each other by virtue of their chemical structure.

Layer: The term layer is used herein to refer to a material that separates one material, component, substrate or environment from another. A layer is often thin in
15 relation to its area and covers the material beneath it. A layer may or may not be thin or flat, but once it is deposited it generally covers the entire surface such that it separates the component or substrate below the layer from the component or environment above the layer.

20 Heterogeneous catalysts: Heterogeneous catalysts enable catalytic reactions to occur with the reactants and catalysts residing in different phases. As used herein, heterogeneous catalysts include, but are not limited to, mixed metal oxides, mixed metal nitrides, mixed metal sulfides, mixed metal carbides, mixed metal fluorides, mixed metal silicates, mixed metal aluminates, mixed metal phosphates, noble metals, zeolites, metal
25 alloys, intermetallic compounds, inorganic mixtures, inorganic compounds, and inorganic salts.

Homogeneous catalysts: Homogeneous catalysts enable catalytic reactions to occur with the reactants and catalysts residing in the same phase. As used herein, homogeneous
30 catalysts include, but are not limited to, catalysts for the polymerization of one or more olefinic or vinyl monomers. The olefinic monomers include, but are not limited to, ethylene or alpha-olefins containing from 3 to 10 carbon atoms, such as propylene, 1-butene, 1-pentane, 1-hexene, and 1-octene. The vinyl monomers include, but are not

materials are formed immediately as the components contact each other on the substrate. In yet another embodiment, the array is formed as previously described, but after the various components are delivered to the substrate, a processing step is carried out which allows or causes the components to interact to form layers, blends, mixtures, and/or materials resulting from a reaction between components. In still another embodiment, two or more components are delivered to the predefined regions on the substrate using fast sequential or parallel delivery techniques such that the components interact with each other before contacting the substrate. The resulting array of materials, each at a discrete and known location on the substrate, comprises layers, blends, mixtures, and/or materials resulting from a reaction between components.

Essentially, any conceivable substrate can be employed in the invention. The substrate can be organic, inorganic, biological, nonbiological, or a combination thereof. The substrate can exist as particles, strands, precipitates, gels, sheets, tubing, spheres, containers, capillaries, pads, slices, films, plates, slides, *etc.* The substrate can have any convenient shape, such as a disc, square, sphere, circle, *etc.* The substrate is preferably flat, but may take on a variety of alternative surface configurations. For example, the substrate may contain raised or depressed regions on which the synthesis of diverse materials takes place. The substrate and its surface preferably form a rigid support on which to carry out the reactions described herein. The substrate may be any of a wide variety of materials including, for example, polymers, plastics, pyrex, quartz, resins, silicon, silica or silica-based materials, carbon, metals, inorganic glasses, inorganic crystals, and membranes. Upon review of this disclosure, other substrate materials will be readily apparent to those of skill in the art. Surfaces on the solid substrate can be composed of the same materials as the substrate or, alternatively, they can be different (*i.e.*, the substrates can be coated with a different material). Moreover, the substrate surface can contain thereon an adsorbent (for example, cellulose) to which the components of interest are delivered. The most appropriate substrate and substrate-surface materials will depend on the class of materials to be synthesized and the selection in any given case will be readily apparent to those of skill in the art. In other embodiments, the substrate can be a series of small beads or pellets. As with the single substrate having an array of materials thereon, each of the individual beads or pellets can be screened for materials having useful properties.

October 18, 1995; "Systems and Methods for the Combinatorial Synthesis of Novel Materials," patent application Serial No. 08/841,423, filed April 22, 1997; and "Discovery of Phosphor Materials Using Combinatorial Synthesis Techniques," provisional patent application Serial No. 60/039,882, filed March 4, 1997; the complete
5 disclosures of which are incorporated herein by reference for all purposes.

In some embodiments of the present invention, after the components have been deposited onto predefined regions on a substrate, they are reacted using a number of different techniques. For example, the components can be reacted using solution based synthesis techniques, photochemical techniques, polymerization techniques, template
10 directed synthesis techniques, epitaxial growth techniques, by the sol-gel process, by thermal, infrared or microwave heating, by calcination, sintering or annealing, by hydrothermal methods, by flux methods, by crystallization through vaporization of solvent, *etc.* Furthermore, each predefined region on the substrate can be heated simultaneously or sequentially using heat sources such as focussed infrared radiation,
15 resistive heating, *etc.* Reactants can, for example, be dispensed to the library of elements in the form of a gas or a liquid. Other useful techniques that can be used to react the components of interest will be readily apparent to those of skill in the art. Additionally, components can react with each other instantly, upon contacting each other, or in the air before contacting the substrate. The components can also form layers, blends or mixtures.
20 in the air or on the substrate, rather than reacting with each other.

Once prepared, the array of resulting materials can be screened for useful properties using the methods described herein. Either the entire array or, alternatively, a section thereof (*e.g.*, a row of predefined regions) can be screened using parallel or fast sequential screening. In some embodiments, a predefined region on the substrate and,
25 therefore, the area upon which each distinct material is synthesized, is smaller than about 25 cm^2 , less than 10 cm^2 , less than 5 cm^2 , less than 1 cm^2 , less than 1 mm^2 , or less than 0.5 mm^2 . In other embodiments, the regions have an area less than about $10,000\text{ }\mu\text{m}^2$, less than $1,000\text{ }\mu\text{m}^2$, less than $100\text{ }\mu\text{m}^2$, or less than $10\text{ }\mu\text{m}^2$. Accordingly, the density of regions per unit area will be greater than $.04\text{ regions/cm}^2$, greater than 0.1 regions/cm^2 ,
30 greater than 1 region/cm^2 , greater than 10 regions/cm^2 , or greater than 100 regions/cm^2 . In other embodiments, the density of regions per unit area will be greater than $1,000\text{ regions/cm}^2$, greater than $10,000\text{ regions/cm}^2$, greater than $100,000\text{ regions/cm}^2$, or greater than $10,000,000\text{ regions/cm}^2$.

heterogeneous or solid state inorganic array elements. Organometallic catalyst libraries which can be screened for useful catalytic properties include, but are not limited to, those described in co-pending U.S. Patent Application Serial No. 08/898,715, filed July 22, 1997, which is hereby incorporated by reference for all purposes.

5 Catalyst libraries comprising inorganic (*e.g.*, heterogeneous and solid state inorganic) materials can also be screened for useful properties using the methods of this invention. Catalyst libraries can comprise powders, impregnated solid supports, inorganic films and monoliths, or crystals that are spatially separated within a substrate system (*e.g.*, wells, flat surfaces). Solid state inorganic materials useful as heterogeneous catalysts are
10 well known in the chemical industry. Heterogeneous catalysts enable catalytic reactions to occur with the reactants and catalysts residing in different phases and include, but are not limited to, mixed metal oxides, mixed metal nitrides, mixed metal sulfides, mixed metal carbides, mixed metal fluorides, mixed metal silicates, mixed metal aluminates, mixed metal phosphates, noble metals, zeolites, metal alloys, intermetallic compounds, inorganic
15 mixtures, inorganic compounds, and inorganic salts. Heterogeneous catalyst systems typically comprise metals, metal oxides, metal sulfides, and other metal salts, can be supported on a carrier (*e.g.*, alumina, silica of controlled particle size and porosity), and can be used in bulk.

Heterogeneous catalysts can be prepared by a number of methods which are
20 well known in the art and include mixing reactive solutions, impregnation of solutions of metal salt precursors onto or into solid carriers, coprecipitation, and mixing colloidal dispersions. These methods yield chemically complex, multicomponent solid products that can be further treated with reducing agents, oxidizing agents and other third components and modifiers to produce optimized materials.

25 Once an array of catalysts is formed, the screening methods of the present invention can be used to characterize the catalytic properties of the various compounds by observing, for example, activity, lifetime and selectivity for a variety of catalytic transformations. For purposes of this invention, a catalyst is defined as any material that accelerates the rate of a chemical reaction and which is either not consumed during the
30 reaction or which is consumed at a rate slower (on a molar basis) than the reaction that is being catalyzed. Examples of catalytic reactions/transformations include, but are not limited to, total oxidations (*e.g.*, the conversion of CO into CO₂ using oxygen, or NO_x for simultaneous reduction of the NO_x), selective oxidations (*e.g.*, epoxidations of olefins),

such that measurements of the heat evolved by one element in the library relative to others within the library reveals trends useful in the characterization of the chemical processes induced by these materials.

According to another embodiment of the invention illustrated in Fig. 1, the
5 relative thermal diffusivities of the different materials on a library are measured, thus providing a measure of the material density, thermal conductivity, and specific heat for the individual materials. The different materials 101 are affixed to a uniform substrate 103, for example using a deposition process. A modulated heat source 105 is directed toward the underside of the library, either directly adjacent to a single element or in such a
10 manner as to simultaneously and uniformly irradiate the entire library. An IR detector 107 scans the library, either by repositioning the detector or by repositioning the library relative to the detector. Detector 107 monitors the temperature change of library materials 101 in response to the modulation of heat source 105. If heat source 105 does not simultaneously and uniformly irradiate the entire library, it must be scanned in conjunction
15 with detector 107, thus insuring that the monitored thermal diffusivities correspond to the same heat input. To maximize the sensitivity of this configuration, substrate 103 should be as thin and thermally transparent as possible.

Fig. 2 illustrates a second configuration of the embodiment shown in Fig. 1. In this configuration, a modulated heat source 201 simultaneously and uniformly irradiates
20 the entire substrate 103, and thus all library materials 101. A position sensitive IR detector array 203 monitors the temperature change of all library elements 101, thus removing the necessity for a translation system.

Fig. 3 illustrates a two-dimensional library 300 of materials according to one embodiment of the invention. The individual library elements are contained within a
25 plurality of reaction wells 301 in a substrate 303. Substrate 303 is placed within a sealed reaction chamber (not shown) which is subsequently filled with selected gases and pressurized. Substrate 303 is then heated *in situ*. Windows 305 and 307 are made of an infrared transparent medium (*e.g.*, BaF₂, CaF₂, NaCl, *etc.*) capable of holding the pressurized gas inside the chamber. Since windows 305 and 307 are transparent, thermal
30 imaging techniques can be used to monitor, in parallel, the heat of reaction of the array under various external conditions.

Measuring the heat of reaction through temperature changes is a useful technique for screening catalytic rate. Though insensitive to products, this method

Example

The following example indicates the use of thermal imaging according to the invention to monitor thermal emission during a polymerization reaction. Fig. 4 illustrates a reaction chamber 400 for monitoring thermal (*i.e.*, infrared) emission at a predefined pressure and temperature. Thus system 400 can be used to screen libraries of potential catalysts for activity under polymerization conditions. Typically a library of catalysts, such as the substrate shown in Fig. 3, is placed in system 400. The catalysts, solvents, initiators, and additional components necessary to carry out the polymerization reaction are placed into wells within thermostatted substrate 303, which is capable of reaching elevated temperatures, such as 100 °C, under an overpressure of gas, such as ethylene gas at 40 psig. The temperature of each well is monitored through an IR transparent window 401 with a position sensitive imaging system 403. Preferably imaging system 403 captures thermal maps of the library at fixed intervals in time. Fig. 5 illustrates a representative thermal map 500. The library imaged in thermal map 500 includes 61 elements. As illustrated, higher temperatures are indicated by an increase in image intensity as well as a change in color from blue to red.

The graph illustrated in Fig. 6 provides the temperature of eleven representative library elements as a function of time. If higher resolution is required, more frequent data points can be obtained simply by decreasing the time intervals between IR images.

Differential Thermal Analysis

Changes in the structure and bonding of a chemical composition during a transition from one thermodynamically stable phase to another results in heat being evolved (exothermic process) or absorbed (endothermic process). Therefore during a phase transition the temperature of the sample of interest may change or the rate of temperature change may increase or decrease. Traditionally, differential thermal analysis is performed in a sealed environment where the temperature of the material being measured is compared to the temperature of a standard material (*e.g.*, α -Al₂O₃) having no phase transition as the temperature is varied over the range of interest. In differential thermal analysis, the temperature of the standard material is subtracted from the

the vibrational character of polymers. For example, structural parameters such as the frequency of methyl, butyl, and ethyl branches in polyethylene can be determined from changes in the peak absorbances in the mid-IR region.

There are several configurations of the invention that can be used to
5 measure the infrared absorption spectrum of a combinatorial library, examples of which are described below.

Infrared Absorption Spectroscopy Using a Monochromatic Source

10 According to one embodiment of the invention, specific molecular vibrations are evaluated by infrared absorption. Because C=C stretch modes have specific absorptions at 1650 and 2200 cm^{-1} , monitoring the relative change in absorption at those frequencies over a library provides a measure of the relative change in the number of C=C bonds in the system. Therefore, the change in absorption reflects structural changes
15 that occur during polymerization, for example during the polymerization of ethylene.

Fig. 7 illustrates a system in which a monochromatic infrared source 700 irradiates a library of compounds 705 contained on a substrate 710. Substrate 710 is made of an infrared transparent material such as BaF_2 , CaF_2 , or NaCl , and may or may not include wells, as shown. Source 700 can be a monochromatic infrared source tuned to a
20 specific wavelength using selective filters, for example, or any other tunable monochromatic source. The intensity of the portion of IR beam 715 passing through library element 705 and substrate 710 is detected as a function of time by an IR sensor 720. IR sensor 720 may be comprised, for example, of either HgCdTe or InSb detectors. By monitoring the infrared absorption as a function of time, the progression of the reaction
25 can be monitored.

Source 700 can be directed through individual library elements one-by-one in a serial fashion, or a large area source beam can be passed through the entire library. Similarly, infrared detection system 720 may be a single infrared detector scanned over the library in a serial manner, or it may be a position sensitive imaging system monitoring the
30 absorption of all of the library elements in a parallel manner.

example using lens 909, prior to interacting with sample 903. Suitable collection optics 911 focuses the IR beam passing through sample 903 onto the FPA of camera 905. Infrared camera 905 captures position sensitive infrared profiles sequentially in time at a rate determined by the desired spectral resolution and spectral bandwidth, preferably at a rate of 60 frames/sec or greater. The sequential intensity profiles are transformed (using Fourier analysis) into a complete infrared spectrum with the aid of computer 907.

Infrared source 901 of the imaging FT-IR setup generally includes a radiation source and signal processing equipment (e.g., interferometer). A typical source is a glowbar or some other heated material capable of producing a polychromatic spectrum covering the infrared region of interest.

In an FT-IR system, light from a point source is rendered parallel by a collimator and passed on to a beamsplitter. The two beams formed by the beamsplitter travel to the mirrors and are reflected back. The beams then recombine at the beamsplitter where they interfere to produce an interferogram that is directed at the combinatorial library. After interacting with the library, the infrared radiation passing through the library is focused onto the detector. The detector records an intensity signal that depends on the path difference imposed by the travel to and from the mirrors and the absorption by the materials in the combinatorial library. The distance from the beamsplitter to the mirrors is arbitrary; what matters is the difference in the lengths of the paths.

One of the mirror arms in the interferometer is moved at a constant velocity, V . When illuminated by a monochromatic source, the detector will see a periodically varying cosine wave. The electrical frequency f of this wave is determined by the rate of change of the path difference dD/dt . Since dD/dt is simply $2V$, f is equivalent to $2nV$. Therefore, a Michelson interferometer can be considered to be a form of frequency transducer that converts optical frequencies which are typically too fast for a detector to monitor down to electrical frequencies that can have any value determined by the mirror velocity V .

The path difference is easily determined with the aid of a laser, for example a HeNe laser. The laser beam is sent through the interferometer concurrently with the IR radiation. As the path difference changes, the monochromatic laser light forms a cosine wave at a detector. By counting the number of maxima (fringes) in the pattern generated by the recombined beam, the path difference can be measured very precisely, as is well known in the art.

compounds. Therefore, the modulated IR radiation from the interferometer preferably interacts with each sample in the library before it reaches the IR camera. There are two different sample configurations that are useful for polymer analysis: (i) post polymerization analysis of polymer films that can be void of solvent and (ii) *in situ* analysis of polymerization reactions where solvent may be present. Both configurations can be performed with transmission spectroscopy. However, the restraints on the samples differ for each configuration due to the detection limits of the FPA and interactions with the solvent.

Post reaction analysis of thin-film libraries is significantly easier than the *in situ* analysis. Aside from eliminating the solvent peaks from the spectrum, the signal to noise ratio is maximized by increasing the integration time on the FPA since the time constraints placed on the system while attempting to track a chemical reaction are eliminated. The signal to noise ratio is further maximized due to the inherent increase in absorption resulting from a high concentration of polymer interacting with the source radiation. A thin-film library can be robotically deposited on a suitable IR transmitting substrate and then imaged in parallel very easily with this system.

Monitoring a polymerization reaction is substantially more complicated. First, a reaction vessel capable of holding the polymer solutions must be constructed with the following criteria: (i) at least one side of the reaction vessel must have an IR transparent material to allow the radiation to pass through the sample; (ii) the general features of a polymerization reactor must be maintained (*e.g.* temperature control, mixing/agitation, *etc.*); and (iii) the thickness and therefore the IR path length of the reaction vessel must be small enough that the radiation is not completely attenuated, but still long enough to allow for a measureable amount of absorption. For example, a 6mm diameter x 10mm long cylinder (having a volume about equal to 0.3cc) in a standard plate is used for the near-IR, and a similar plate design with a cylinder having a 1mm path length is used for the mid-IR. An example of one design is schematically illustrated in Fig. 3.

The sample chamber should be isolated from stray IR radiation. For example, a person walking into the area where the experiment is being performed provides a measurable amount of reflected heat radiation that may be picked up by the FPA. A closed sample chamber similar to those found in commercial FT-IRs is typically acceptable.

applications and publications, are incorporated herein by reference for all purposes.

4 enclosing said array in a chamber;
5 enclosing a standard material in said chamber;
6 monitoring an infrared emission from each of said materials of said array
7 and of said standard material with an infrared camera while at least one environmental
8 condition within said chamber is varied, wherein said infrared camera outputs a series of
9 signals corresponding to a temperature of each of said materials as a function of time, and
10 wherein said environmental condition is selected from the group consisting of chamber
11 temperature, chamber pressure, and chamber gas composition; and
12 calculating a temperature difference between each of said materials of said
13 array and said standard material.

1 6. A method of monitoring the infrared absorption spectrum of a
2 library of materials contained in an array, said method comprising the steps of:
3 providing a substrate;
4 synthesizing said array of materials on said substrate;
5 irradiating said array of materials with a monochromatic infrared radiation
6 source; and
7 monitoring material absorption for each of said materials of said array as a
8 function of time.

1 7. The method of claim 6, wherein said monochromatic infrared
2 radiation source sequentially irradiates said materials of said array.

1 8. The method of claim 6, wherein said monochromatic infrared
2 radiation source simultaneously irradiates said materials of said array.

1 9. A method of monitoring the infrared absorption spectrum of a
2 library of materials contained in an array, said method comprising the steps of:
3 providing a substrate;
4 synthesizing said array of materials on said substrate;
5 irradiating said array of materials with a polychromatic infrared radiation
6 source;
7 filtering radiation passing through said array of materials with at least one

1 15. A system for monitoring the heats of reaction of a combinatorial
2 array of materials, comprising:
3 an IR transparent substrate containing said combinatorial array of materials;
4 a reaction chamber enclosing said IR transparent substrate;
5 at least one reactant gas, wherein said reactant gas is coupled to said
6 reaction chamber through a valve; and
7 an infrared camera imaging said combinatorial array of materials, wherein
8 said infrared camera outputs a series of signals corresponding to an emission intensity as a
9 function of time of at least one activated material of said combinatorial array of materials.

1 16. The system of claim 15, further comprising a heat source capable of
2 selectively heating at least one material of said combinatorial array of materials to a
3 predefined temperature.

1 17. The system of claim 16, wherein said heat source is selected from
2 the group consisting of focussed infrared radiation sources and resistive heating elements.

1 18. The system of claim 15, further comprising:
2 a standard material within said reaction chamber, said standard material
3 within a field of view of said infrared camera; and
4 a processor for calculating a temperature difference between said materials
5 of said combinatorial array and said standard material.

1 19. The system of claim 18, further comprising means for varying an
2 environmental condition within said reaction chamber, wherein said environmental
3 condition is selected from the group consisting of chamber temperature, chamber pressure,
4 and chamber gas composition.

1 20. A system for monitoring the infrared absorption of each of a
2 plurality of materials contained on a combinatorial array of materials, comprising:
3 an IR transparent substrate containing said combinatorial array of materials;
4 an infrared radiation source, wherein said radiation source sequentially

8 focuses radiation from said combinatorial array of materials onto said focal plane array;
9 and
10 a processor coupled to said infrared camera, said processor transforming
11 sequential intensity profiles captured by said camera into infrared spectra using Fourier
12 analysis.

1 27. The system of claim 26, wherein said radiation source is further
2 comprised of an interferometer.

1 28. The system of claim 27, wherein a mirror within said interferometer
2 moves at a constant velocity resulting in a continuous output.

1 29. A system for monitoring the infrared emission of each of a plurality
2 of materials contained on a combinatorial array of materials, comprising:
3 a substrate containing said combinatorial array of materials;
4 an infrared radiation source emitting radiation of at least a first wavelength.
5 wherein said radiation source irradiates said plurality of materials; and
6 an infrared detection system monitoring infrared emission of at least a
7 second wavelength as a function of time for each of said plurality of materials.

1 30. A method of characterizing a relative thermal diffusivity for a
2 plurality of materials, comprising the steps of:
3 providing a thermally uniform substrate;
4 synthesizing said plurality of materials on a first surface of said substrate;
5 irradiating a second surface of said substrate with an infrared source;
6 modulating said infrared source; and
7 monitoring a temperature change associated with each of said plurality of
8 materials as a function of time, said temperature change indicative of said relative thermal
9 diffusivity of said plurality of materials.

1 31. A system for characterizing a relative thermal diffusivity for a
2 plurality of materials, comprising:
3 a thermally uniform substrate containing said plurality of materials on a first

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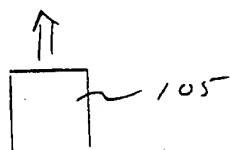
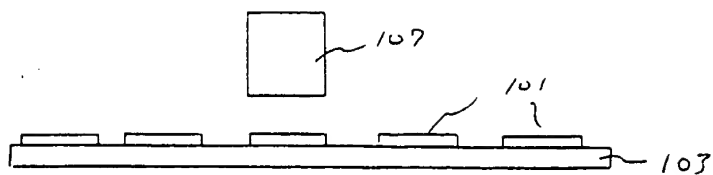


FIG. 1

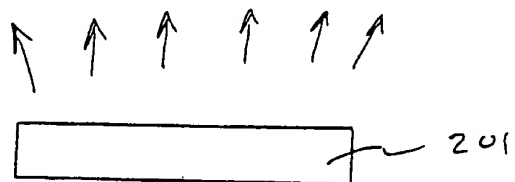
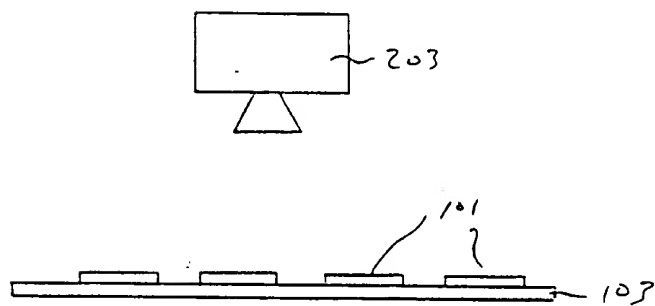


FIG. 2

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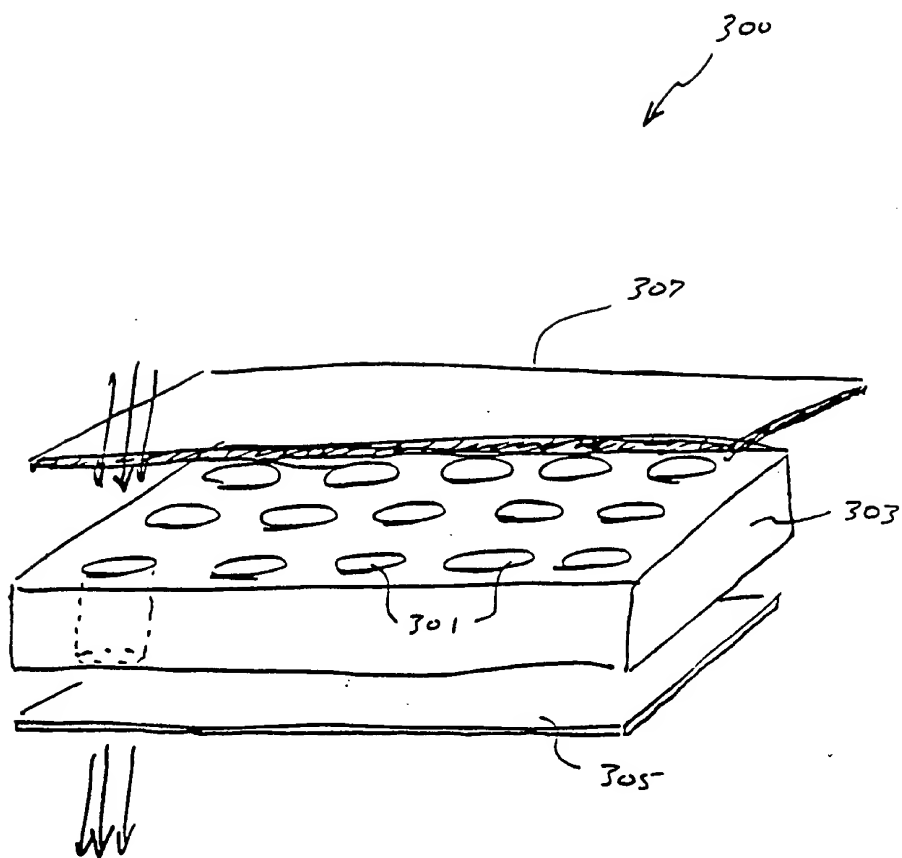


FIG. 3

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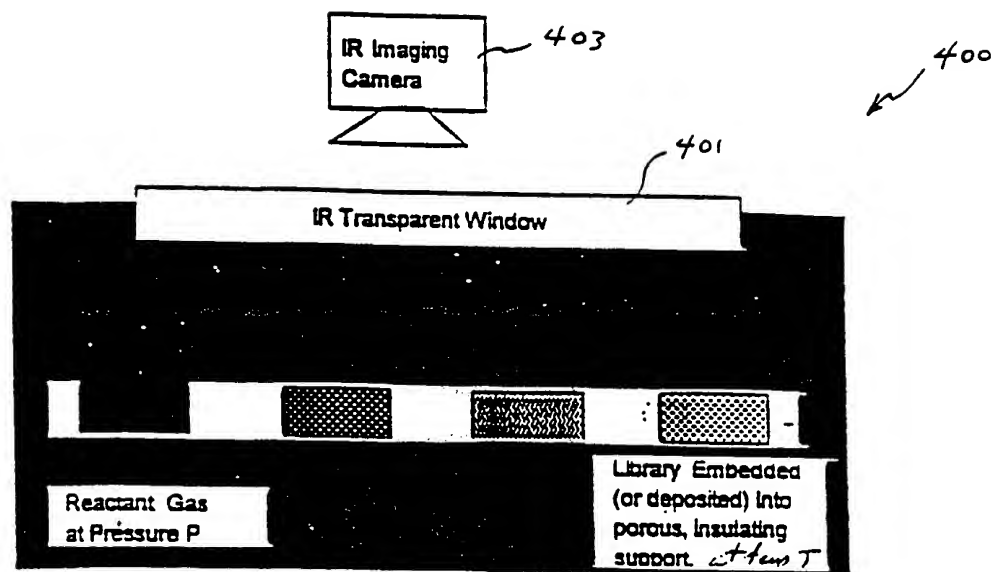


Fig 4

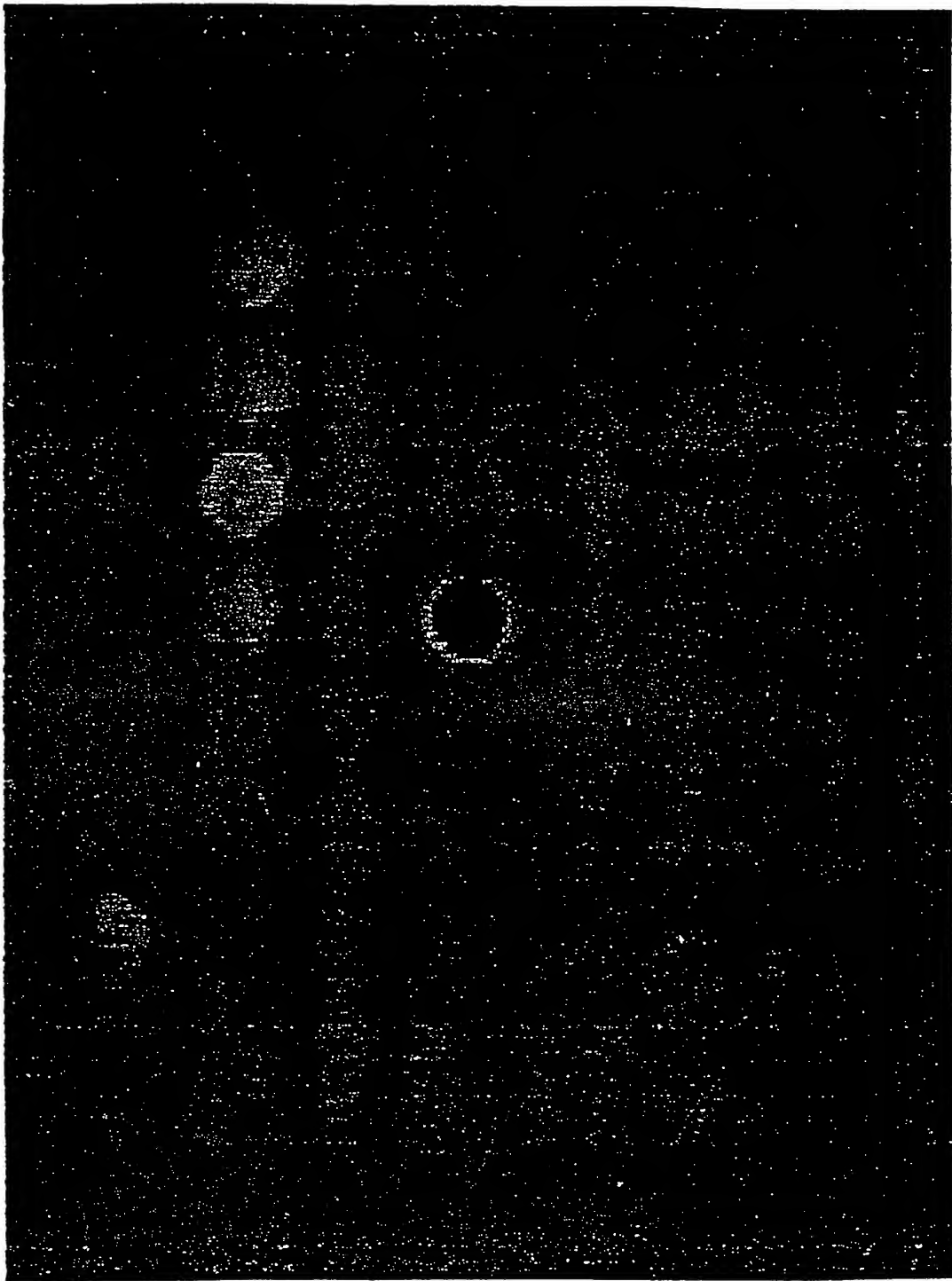


FIG. 5

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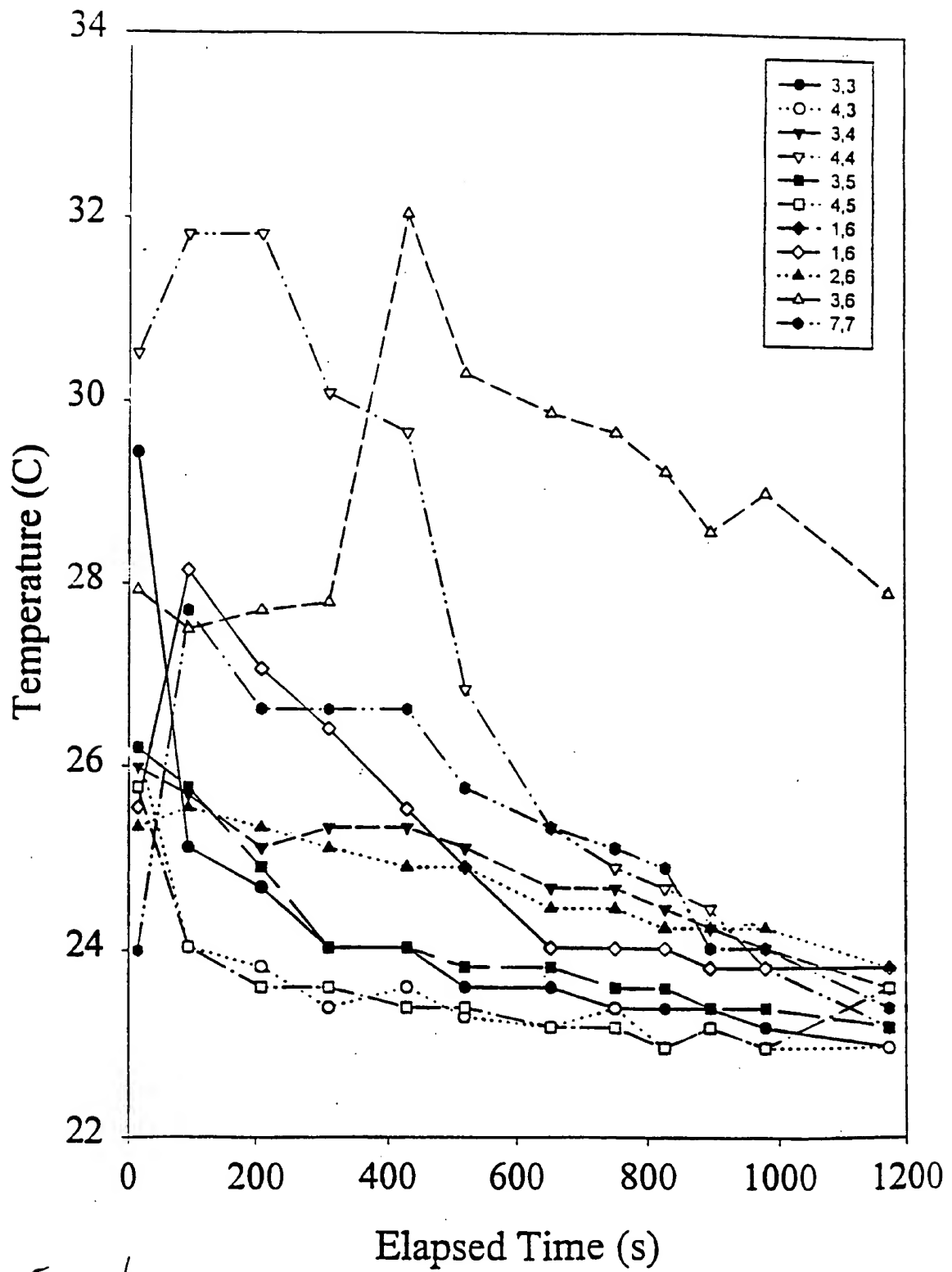


Fig. 6

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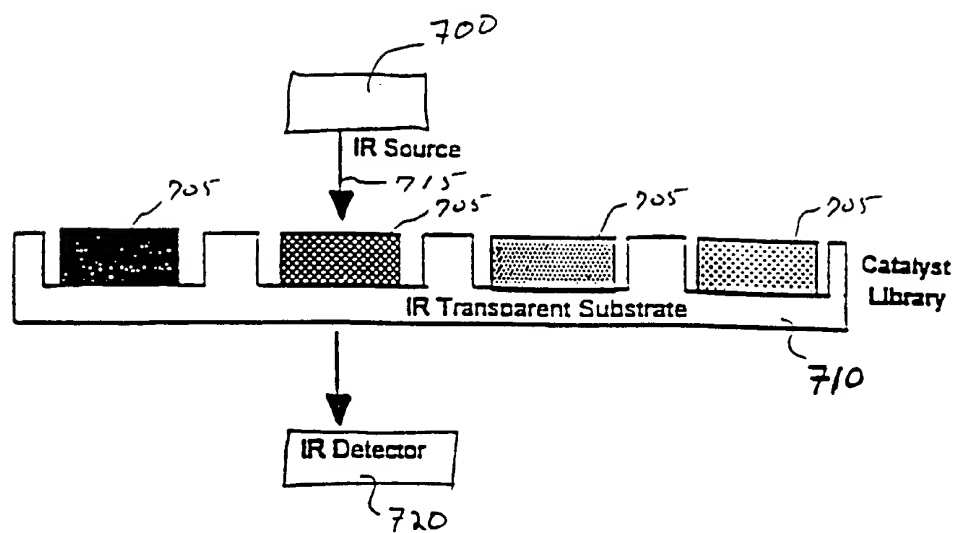


Fig. 7

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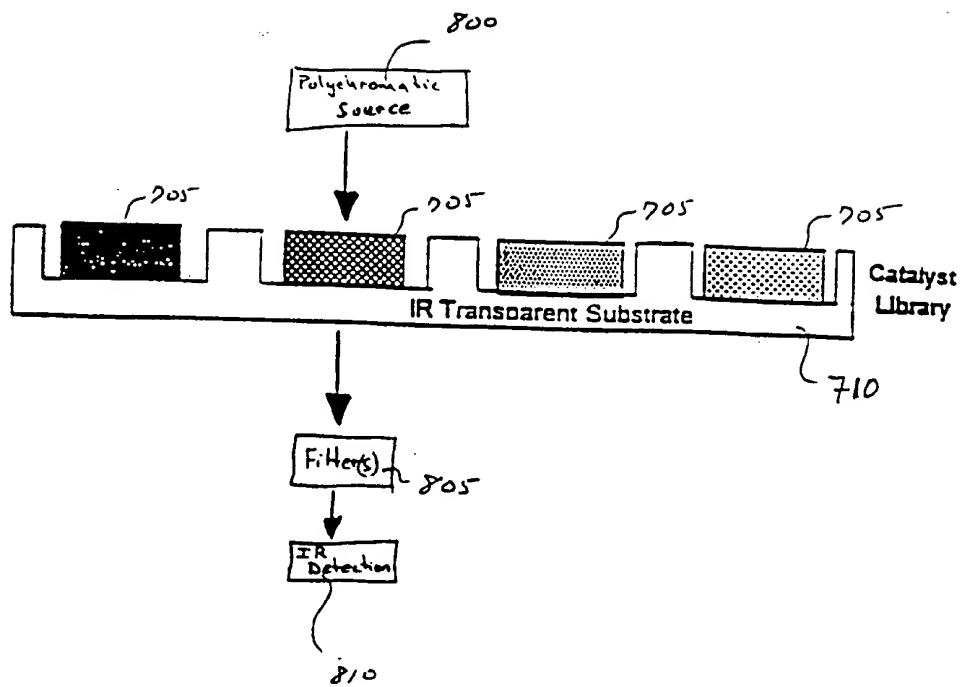


Fig. 8

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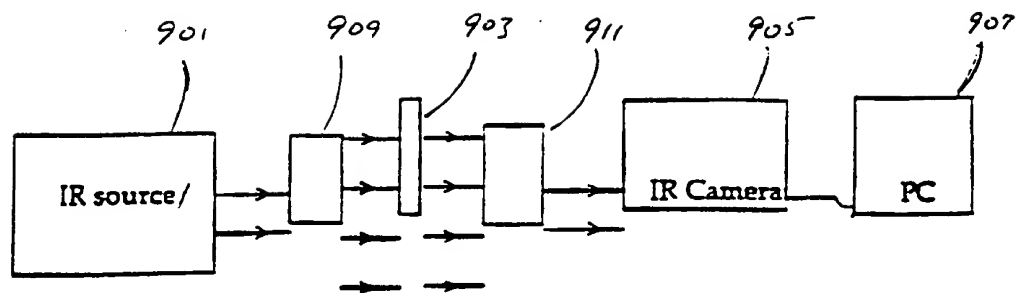


Fig. 9

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/18177

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 G01N21/35 G01N25/72

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	MOATES F. C. ET AL: "Infrared thermographic screening of combinatorial libraries of heterogeneous catalysts" IND. ENG. CHEM. RES. , vol. 35, pages 4801-4803, XP002054589 see page 4801	1-32
A	HARDISTY H ET AL: "Thermal imaging in electronics and rotating machinery" BRITISH JOURNAL OF NON-DESTRUCTIVE TESTING, FEB. 1994, UK, vol. 36, no. 2, ISSN 0007-1137, pages 73-78, XP002054590 see page 73 see page 75 - page 76; figures 2,6	1-32

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

4 February 1998

Date of mailing of the international search report

20.02.98

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5344236 A	06-09-94	NONE	
US 5200023 A	06-04-93	NONE	
EP 0535881 A	07-04-93	US 5294198 A	15-03-94
		JP 5312636 A	22-11-93
GB 2194847 A	16-03-88	NONE	